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Document Title
ACUTE INHALATION TOXICITY (LC50) IN THE MALE ALBINO RAT -- DIPHENYL METHANE DIISOCYANATE

Chemical Category
DIPHENYL METHANE DIISOCYANATE (1321-38-6)

24298

International Research and Development Corporation

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SPONSOR: The Upjohn Company

COMPOUNDS: PAPI
MDI, Pure, Distilled

SUBJECT: Acute Inhalation Toxicity (LC_{50}) in the Male Albino Rat.

Francis X. Wazeter, Ph.D.
Director of Research
International Research and
Development Corporation

Collaborators:

R. H. Buller, Ph.D., Director of Pharmacology
R. G. Geil, D.V.M., Director of Pathology
R. T. Jacobs, D.V.M., Toxicologist

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203-004

I. SYNOPSIS

The test compounds were examined for acute inhalation toxicity (LC_{50}) using the male albino rat. All compounds were tested in the vapor form. Six rats for every concentration of each respective test agent were used.

An LC_{50} for PAPI could not be determined, since the physical constants of PAPI and the experimental protocol did not permit such a calculation.

While lethal levels were established for MDI, Pure, Distilled, an exact LC_{50} could not be calculated from the data. The approximate LC_{50} lies between 172 and 187 mg./L.

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II. COMPOUNDS

The test compounds were received from the Upjohn Company, Carwin Division, North Haven, Connecticut, on August 24 and December 24, 1964.

Each of the four test compounds was sealed in a glass bottle and was identified as follows:

Compound	Code No.	Description
PAPI	2B-14-65	Dark brown viscous liquid
MDI, Pure, Distilled	---	Pale orange moist crystals

III. METHODS

A. General Procedure:

Male, albino rats of the Spartan Sprague-Dawley strain and weighing from 200 to 300 grams were used. The rats were individually housed in wire mesh cages elevated above the droppings and maintained in air-conditioned and humidity-controlled quarters throughout the pre-exposure and post-exposure periods. Food and water were available ad libitum except during the exposure period.

Body weights on all animals used were obtained prior to exposure to each respective agent and at 7 and 14 days after exposure.

All of the rats were observed for evidence of pharmacodynamic and/or toxic signs during the exposure period; for an additional period of several hours immediately after exposure; and daily for 13 days thereafter.

Animals which failed to survive the post-exposure observation period were necropsied and examined. All rats which survived to the termination of the 14-day observation period were sacrificed by means of an intraperitoneal injection of sodium pentobarbital and also necropsied and examined.

B. Compound Administration:

All of the compounds in these tests were analyzed in vapor form. This was accomplished by heating each respective compound in a flask on a water or oil bath at the desired temperature to produce vapors.

The vapors thus formed were carried into the exposure chamber containing the rats by use of an air source produced by a compressor. Prior to entrance into the evaporating flask containing the test agent, the air was passed through a glass wool filter and two drying tubes containing calcium chloride to clean and dry it.

The concentration of the vapors of each test agent carried by the inflowing air could be varied either by changing the volume of the inflow of air, or by altering the temperature of the bath producing the vapors, or as in the case of PAPI , by altering the speed of infusion of the test materials into the evaporating chamber with an infusion pump. Upon occasion, a second air source was introduced into the line carrying the vapors of a given agent into the exposure chamber to aid in further controlling the concentration of a given test material.

The rats were divided into groups of six animals each. One group was used at each respective concentration of each test agent analyzed.

For exposure purposes, a nine-liter air-tight chamber was used. All animals were exposed for one continuous hour to the vapors of each respective test agent.

1. PAPI:

This agent was injected into the distillation flask with a Harvard Infusion Pump (Model No. 600-910). The distillation flask was heated to a temperature of approximately 150 ± 2° Centigrade with an oil bath. The vapors thus formed were carried into the exposure chamber with a controlled inflow of air, as previously described, at 10 liters per minute..

Two groups of six rats each were thus exposed to analyzed concentrations of PAPI of 14.7 or 17.0 micrograms per liter (mcg./L.). Higher concentrations of PAPI could not be obtained by increasing the inflow of the compound with the infusion pump, and the degree of heat used could not be increased without exceeding the decomposition temperature of the agent. Furthermore, reduction of airflow produced

condensation (fallout) within the exposure chamber. Thus, only two concentrations of PAPI were analyzed.

The table below describes the experimental variables used in this test.

PAPI

Experimental Variables:

Infusion Speed ml./min.	Oil Bath Temp. °C.	Airflow (L/M)	Analyzed Exposure Chamber Concen. (mcg./L.)
0.194	150	10	14.7
0.494	150	10	17.0

2. MDI, Pure, Distilled:

MDI, Pure, Distilled was evaluated at analyzed concentrations of 0.6, 80.8, 162.0, 171.5, 186.6, 562.5 and 1530 mcg./L., using 6 rats at each respective concentration.

The vapor for the lowest concentration analyzed (0.6 mcg./L.) was produced by passing air through the test agent which was contained in a flask on an oil bath. The oil bath was maintained at a temperature of 100 ± 2° C. The airflow into the evaporating chamber was passed directly into the exposure chamber at a speed of one liter per minute.

All succeeding concentrations were produced in a similar manner, except that the test agent was heated to a temperature of approximately 200 ± 2° C. Airflow through the evaporating chamber was varied between 1 and 2 liters per minute. Further dilution of the air containing the vapors was accomplished with a second air source which was interposed into the system just prior to its entry

into the exposure chamber. Airflow from this second source was varied from 0 to 10 liters per minute. By varying the airflow from the second source, the concentration of the vapors entering the exposure chamber could be controlled. The following table describes the experimental variables and the concentrations of MDI thus produced.

MDI, Pure, Distilled

Experimental Variables:

Oil Bath Temp. °C.	Airflow (Liters/Minute) Primary Source	Secondary Source	Total	Analyzed Exposure Chamber Concen. (mcg./L.)
100	1.0	0.0	1.0	0.6
200	1.0	10.0	11.0	80.8
200	1.5	7.0	8.5	162.0
200	1.0	6.0	7.0	171.5
200	1.5	6.0	7.5	186.6
200	2.0	2.0	4.0	562.5
200	2.0	0.0	2.0	1530.0

C. Analytical Methods

Prior to the exposure of the animals to varying concentrations of each test agent, calibration curves were prepared for each substance by the following method: Serial dilution of a known concentration of each respective test agent in the reagent (0.5 per cent p-dimethylaminobenzaldehyde in 50 per cent glacial acetic acid) were prepared. After maximum color development had occurred, each dilution was read in a Coleman spectrophotometer at a wave length of 425 millimicrons, using a reagent blank to balance the instrument.

The optical densities thus obtained were plotted against the concentrations in mcg./ml. for each test agent. The resultant curves obtained were used to determine the concentration in mcg./L. of subsequently obtained samples of atmospheric concentrations from the exposure chamber of each agent during a given exposure.

IV. RESULTS

A. Pharmacodynamic and/or Toxic Signs:

1. PAPI:

a. 14.7 and 17.0 mcg./L.:

All rats at both concentrations of PAPI appeared essentially normal throughout the one-hour exposure period and the 14-day post-exposure observation period. Slight salivation and erythema were observed during the exposure period in both groups of rats. All rats at both concentrations used survived the 14-day observation period.

2. MDI, Pure, Distilled:

a. 0.6 mcg./L.:

Signs seen during the exposure included a general slight erythema and restlessness. Five-of-six exhibited slight salivation and 2-of-6 showed slight nasal porphyrin discharge. All rats in this group appeared normal the following day and remained so until necropsy.

b. 80.8 mcg./L.:

During the exposure the rats exhibited salivation, excessive lacrimation and clear nasal drip, dyspnea, escape behavior, and slight nasal porphyrin discharge. No signs were seen from the day following the exposure until necropsy. All rats survived the 14-day observation period.

c. 162 mcg./L.:

Signs seen during this exposure were similar to those seen at the 80.8 mcg./liter level, but appeared among the rats much earlier, and were more marked at the termination of the exposure. Again, all 6 rats appeared essentially normal

from the day following the exposure until necropsy and all survived the observation period.

d. 171.5 mcg./L.:

Signs recorded during this exposure included those noted above at lower concentrations, plus a slight increase in activity during the initial few minutes. One-of-six rats showed marked nasal porphyrin at the termination of the exposure. All rats appeared essentially normal from the day following the exposure until necropsy and all survived to termination of the test period.

e. 186.6 mcg./L.:

In addition to the salivation, excessive lacrimation, clear nasal drip, and dyspnea, previously mentioned, an increase in grooming activity, and eye-squint were seen during this exposure. At the termination of this exposure, all rats exhibited salivation and dyspnea, and 3-of-6 showed muscle flaccidity. Three-of-six rats died overnight after the exposure. The day following the exposure, 1-of-3 showed dyspnea and nasal and ocular porphyrin, and 2-of-3 showed hypoactivity. The 4th mortality occurred 26 hours after the exposure. From the 2nd post-exposure day on, the 2 survivors appeared essentially normal.

f. 562.5 mcg./L.:

Within 10 minutes after initiating this exposure, the exposure chamber was completely filled with "fog". Marked ptyalism, dyspnea, eye-squint, excessive lacrimation, and increased grooming were recorded. In addition, after 55 minutes, the eyes appeared dark and the exposed skin (ears and paws) appeared cyanotic. Inspection of the rats immediately after the exposure revealed

dyspnea, salivation and cyanosis, all of which lasted throughout the balance of the day. Six-of-six mortalities occurred overnight.

g. 1530.0 mcg./L.:

During this exposure, the test chamber again became filled with "fog" during the first few minutes. Gross observations were similar to those recorded for the 562.5 level. Eye-squint advanced to eye-closure and the dark appearance of the eyes and the cyanotic condition of the exposed skin was seen during exposure and at termination of the exposure period. Three-of-six died during the exposure, and the remaining 3 rats within one hour thereafter.

B. Body Weights (Table 2):

1. PAPI:

Rats exposed to an analyzed atmospheric concentration of PAPI of 14.7 mcg./L. showed essentially normal body weight gains. Those rats at the 17.0 mcg./L. level showed a very slight inhibition of body weight gain during the first week only.

2. MDI, Pure, Distilled:

Rats exposed to an analyzed concentration of 0.6 mcg./L. of MDI, Pure, Distilled, showed normal body weight gain during the 2-week period of observation. However, the average body weight gain for the surviving rats of the other 6 groups exposed to the vapors of this agent appeared to be inhibited for the first week.

C. Necropsy Examination:

1. Mortalities:

Necropsies made on those rats that died during the 2-week period of observation revealed the following:

a. PAPI:

No Mortalities.

b. MDI, Pure, Distilled:

(1) 186.6 mcg./L.: Four-of-four exhibited hydrothorax and lungs with edema and congestion; 1-of-4, lungs with severe hemorrhages.

(2) 562.5 mcg./L.: Six-of-six showed hydrothorax and lungs with generalized congestion and edema.

(3) 1530.0 mcg./L.: Six-of-six showed lungs with severe generalized hemorrhage and edema throughout.

2. Survivors:

Necropsies made on those rats which survived the 2-week period of observation revealed the following:

a. PAPI:

(1) 14.7 mcg./L.: Four-of-six, no gross lesions; 1-of-6, lung with 2 mm. dark area; 1-of-6, lungs with 6 mm. areas of congestion.

(2) 17.0 mcg./L.: Four-of-six, no gross lesions; 2-of-6, lungs with 6-10 mm. areas of congestion.

b. MDI, Pure, Distilled:

(1) 0.6 mcg./L.: Four-of-six, no gross lesions; 2-of-6, lungs with 10 mm. areas of congestion.

(2) 80.8 mcg./L.: Five-of-six, no gross lesions; 1-of-6, lung with 6-15 mm. areas of hyperemia.

(3) 162 mcg./L.: One-of-six, no gross lesions; 2-of-6, lungs with 2 mm. red foci; 1-of-6, lungs with two 6 mm. areas of congestion.

(4) 171.5 mcg./L.: No gross lesions seen.

(5) 186.6 mcg./L.: One-of-two, no gross lesions and 1-of-2, a lung with a 2 mm. red foci.

D. Acute Inhalation Toxicity (LC_{50}):

1. PAPI:

It was not possible to achieve an LC_{50} for PAPI.

2. MDI, Pure, Distilled:

Data obtained from the exposures of 7 groups of 6 rats each to 7 different analyzed atmospheric concentrations of MDI, Pure, Distilled vapors does not permit the calculation of an LC_{50}. However, inspection of the levels employed and the mortalities obtained reveals that the LC_{50} is approximately 178 mcg./L.

E. Analytical Results:

The analysis of the actual chamber concentrations of the agents used in these studies at the various concentrations employed were obtained by interpolation from the values appearing in Table 1. In actual practice, graphs were constructed for each individual agent by plotting the data appearing in Table 1. Actual concentrations in the exposure chamber were calculated by obtaining optical densities of 425 millimicrons as previously described under methods, entering the table at the respective density obtained and reading the concentration indicated.

Acute Inhalation Toxicity Studies in the Rat.

TABLE 1. Calibration Curves.

	Optical Densities																
	0.05	0.10	0.15	0.20	25	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85
Compound	Concentration, mcg./ml.																
PAPI	0.3[illegible]	0.53	0.75	1.00	1.27	1.50	1.77	2.00	2.26	2.54	2.90	3.30	3.77	4.37	5.25	6.20	-
MDI, Pure	0.10	0.19	0.30	0.40	0.53	0.62	0.77	0.90	1.04	1.22	1.40	1.58	1.77	2.00	2.35	3.00	4.25

Acute Inhalation Toxicity Studies in the Rat.

TABLE 2. Average Body Weights, Grams.

Test Compound Concentration (mcg./L.)	Control	7 Days	14 Days
PAPI:			
14.7	217	271	301
17.0	261	274	304
MDI, Pure, Distilled:			
0.6	223	279	303
80.8	273	277	323
162.0	263	282	319
171.5	272	274	323
186.6	268	259[a]	305[a]
562.5	292	-	-
1530.0	289	-	-

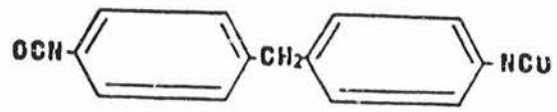
a - 2 rats only

Acute Inhalation Toxicity Studies in the Rat.

TABLE 3. Mortality Data in the Male Albino Rat.

Analyzed Atmospheric Concentration mcg./L.	Time of Death - Days Post-Exposure No. Died/No. Exposed															LC50 and Confidence Limits (mcg./L.)
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total	
PAPI:																	
14.7																0/6	None
17.0																0/6	Possible
MDI, Pure:																	
0.6																0/6	
80.8																0/6	
162.0																0/6	Approximately
171.5																0/6	178
186.6	3/6	1/3														4/6	
562.5	6/6															6/6	
1530.0	6/6															6/6	

MDI



Isocyanic acid, methylenedi-*p*-phenylene ester $C_{15}H_{10}N_2O_2$
4,4'-Diisocyanatodiphenylmethane
Diphenylmethane 4,4'-diisocyanate
Methylene bis(4-phenyl isocyanate)
4,4'-Methylenediphenyl isocyanate
Methylenedi(*p*-phenylene isocyanate)

The manufacture of MDI begins with the condensation of aniline and formaldehyde to form methylenedianiline. Reaction of the methylenedianiline with phosgene yields MDI which, in this "crude" (undistilled) form, may be used for the manufacture of rigid foam. "Crude" MDI may be distilled through several intermediate grades to a high-purity material. The several intermediate grades give varying properties to the end products -- rigid foams or solid elastomers.

MDI is diphenylmethane diisocyanate or methylene bisphenylisocyanate. MDI commercial products contain some of the o,p-isomer, but the chief constituent is p,p-diphenylmethane diisocyanate.

The following data apply for commercial samples of MDI:

Molecular Weight	250.3
Flash Point (COC)	425°F (218°C)
(Closed Cup)	390°F (200°C)
Fire Point	>392°F (200°C)
Boiling Point	597°F (314°C)*
Freezing Point	100°F (38°C)
Specific Grafity of Liquid	1.23 @ 77°F (25°C)
Vapor Density (Air = 1)	
Odor Threshold (Vapor)	0.4 ppm

Vapor Pressure

Temp.°F	Temp.°C	mm Hg.
50	10	.00014
77	25	.00029
100	38	.0006
150	66	.0025
200	112	.010
250	122	.042
300	150	.150

* Decomposes (polymerizes) at about 450°F (232°C).
Decomposes rapidly above 525°F (274°C).

Effects of Inhalation

Slight inhalation toxicity, histologic changes (20).

Effects of Ingestion

The acute oral LD_{50} value for MDI was determined to be greater than 10,000 mg/kg of body weight (20).

A single oral lethal dose has been determine as 31.69 grams/kg (22).

Subacute oral toxicity testing has been done with negative results. Rats exposed for 5 days at 5 grams/kg/day survived (18).

Effects on the Skin

Rabbit Skin Irritation (23): Undiluted MDI applied producing mild irritation which cleared in 5 days. No gross pathology was evident 8 days after testing. Irritation considered minimal.

Effects on Eyes

Rabbit Eye Irritation (23): 1 mg/eye of 10% MDI produced mild inflammation and lacrimation. No gross pathology observed 3 hours after testing. Irritation considered minimal.

A summary of MDI toxicity is tabulated below:

Acute oral LD_{50} (rat) mg/kg	>10000
Single oral lethal dose, grms/kg	31.7
Single skin lethal dose, grms/kg	>30
Subacute oral tox., deaths/no. fed . . .	0/5
Primary skin irritation	None
Eye injury or irritation	Slight
Inhalation toxicity, histologic changes	Slight
Sensitization response potential	Yes

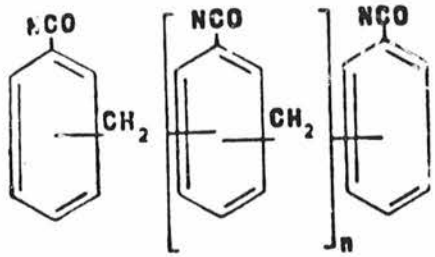
18. ACGIH, Documentation of Threshold Limit Values for Substances in Workroom Air, (1976), ACGIH, P.O. Box 1937, Cincinnati, Ohio 45201.

20. Woolrich, P.F. and Rye, W.A., J. Occ. Med., 11, p. 184, (1969).

21. Henck, J.W. et al., Toxicology Research Lab., Dow Chemical Co., Midland, Michigan, (February, 1976).

22. Toxicity and Safe Handling of Isocyanates, Mobay Chem. Co., Pittsburgh.

23. Hazelton Labs. Inc., Contract DA-18-035-AMC-345-A, (March, 1966).



PAPI® (polymeric Isocyanate)
("Crude" MDI)
(Polymeric MDI)
(Polymethylene Polyphenyl Isocyanate)

PAPI is 50% MDI and 50% MDI oligomers and has an average composition of a trifunctional material. It is a dark, amber, viscous, liquid with very low volatility and a slower reactivity rate than many common aromatic diisocyanates.

The following data apply for commercial samples of PAPI®:

Molecular Weight:	400
Flash Point (COC):	425°F (218°C)
(Closed Cup):	392°F (200°C)
Fire Point:	392°F (200°C)
Boiling Point:	625°F (329°C)
Freezing Point:	50°F (10°C)
Specific Gravity of Liquid:	1.23 @ 77°F (25°C)
Vapor Density (Air = 1):	8.5
Odor Threshold (Vapor):	0.4 ppm

Vapor Pressure	Temp.°F	Temp.°C	mm Hg.
	50	10	.00006
	77	25	.00016
	100	38	.0002
	150	66	.001
	200	112	.004
	250	122	.017
	300	150	.07

PAPI (cont)

° Acute Inhalation Exposure

Ten male albino rats exposed to PAPI vapor (est. concentration, 0.2 ppm) for 8 consecutive hours. No statistically significant alterations in group body weight were observed up to 14 days; no apparent harmful effects observed during exposure or necropsy (20).

A group of 6 male albino rats survived a 7-hour exposure with no apparent ill effects to air near saturation with vapor of polymeric isocyanate at room temperature (est. concentration 0.2 ppm (24).

° Subacute Inhalation Exposure

Eighteen male albino rats were exposed for 30 minutes, once each day, 5 days each week, for 2 weeks to PAPI vapors at analyzed atmospheric concentrations of 0.196, 0.645 or 2.580 ppm. Six rats were used at each respective concentration.

No compound-related adverse changes were found with respect to body weight gains, hematology, or gross and microscopic pathological findings (20).

CERTIFICATE OF AUTHENTICITY

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